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Effect of allergen avoidance on development of allergic disorders in infancy

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There is much evidence that the development of allergic disorders may be related to early exposure of allergens, including those in breastmilk. We have tried to find out whether avoidance of food and inhaled allergens in infancy protects against the development of allergic disorders in high-risk infants.

In a prenatally randomised, controlled study 120 infants with family history of atopy and high (>0·5 kU/l) cord-blood concentrations of total IgE were allocated randomly to prophylactic and control groups. In the prophylactic group (n=58), lactating mothers avoided allergenic foods (milk, egg, fish, and nuts) and avoided feeding their infants these foods and soya, wheat, and orange up to the age of 12 months; the infants' bedrooms and living rooms were treated with an acaricidal powder and foam every 3 months, and concentrations of *Dermatophagoides pteronyssinus* antigen (*Der p* I) in dust samples were measured by enzyme-linked immunosorbent assay. In the control group (n=62), the diet of mothers and infants was unrestricted; no acaricidal treatment was done and *Der p* I concentrations were measured at birth and at 9 months. A paediatric allergy specialist unaware of group assignment examined the infants for allergic disorders at 10–12 months. Odds ratios were calculated by logistic regression analysis for various factors with control for other confounding variables. At 12 months, allergic disorders had developed in 25 (40%) control infants and in 8 (13%) of the prophylactic group (odds ratio 6·34, 95% confidence intervals 2·0–20·1). The prevalences at 12 months of asthma (4·13, 1·1–15·5) and eczema (3·6, 1·0–12·5) were also significantly greater in the control group. Parental smoking was a significant risk factor for total allergy at 12 months whether only one parent smoked (3·97, 1·2–13·6) or both parents smoked (4·72, 1·2–18·2).

Reduced exposure of infants to allergens in food and in housedust lowered the frequency of allergic disorders in the first years of life. Passive smoking is an important risk factor that should be addressed in any prophylactic programme.

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Introduction

In infancy, a family history of atopy is the most important predictor of risk of allergic disorders such as allergic asthma and atopic eczema. A high cord-blood concentration of IgE may also be useful in predicting atopy.[1] There is evidence that immediate hypersensitivity in later life depends on allergenic factors encountered in infancy.[2–5] Sporik and colleagues' study[6] suggests that the development of sensitivity to housedust-mite antigen and the symptoms and severity of asthma in later childhood are directly related to exposure to the antigen in infancy, and infants exposed to cats from birth show increased sensitisation to cat dander.[7] Parental smoking and household overcrowding may be contributing factors.[8,9] Among infants who first receive egg yolk at the age of 3 months intolerance of this food is common, whereas intolerance is rare when egg yolk is introduced at 9 months or later.[10] In 1936, Grulee and Sanford[11] showed a seven-fold increase in eczema in babies fed cows' milk. However, the subject remains controversial.[12]

Small amounts of protein ingested by the mother are secreted unchanged into breastmilk.[13,14] In this way potentially allergenic food eaten by the mother can be transferred to the infant and can cause sensitisation. Thus, maternal dietary restriction during lactation seems to be important.[15–17] We have tried to find out whether avoidance of food and housedust-mite allergens in early life protects against the development of allergic disorders in at-risk infants.

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Subjects and methods

This was a prospective, prenatally randomised, controlled study; assessment was done by observers unaware of group allocation. The prenatal inclusion criteria were dual heredity (allergic disease in both parents, one parent and one sibling, or two siblings) or single heredity (allergic disease in one parent or sibling); for the latter infants cord-blood IgE had to be high (>0·5 kU/l). Between March, 1990, and February, 1991, a research nurse explained the study to all pregnant women (1116) in one district hospital at their last antenatal visit. 504 (45%) reported a history of allergic disease (previously diagnosed asthma, atopic eczema, allergic rhinitis, or food allergy) in themselves, their partners, or their children. 301 (60%) agreed to take part in the study and gave informed consent. 143 mothers were randomly allocated to the prophylactic group, which was instructed about avoiding allergens, and 158 to the control group, based on a computer-generated list of random numbers. Odd numbers were assigned to the control group and even numbers to the prophylactic group.

Total IgE was measured by enzyme-linked immunoassay (Ultra, Pharmacia, Uppsala, Sweden), which can detect 0·2 kU/l to 50 kU/l. The IgE result was available within a few days of birth. The diet of mothers and infants in the prophylactic group was restricted until that time. 162 of the 194 infants with single heredity (prophylactic 72, control 90) were excluded since their cord-blood IgE was less than the entry requirement. 3 premature infants (prophylactic 2, control 1) were also excluded because of their special dietary requirements. Of 301 women randomised before birth, the infants of 136 met the inclusion criteria and entered the study.

16 infants did not complete follow-up (prophylactic 11, control 5). 1 infant in the prophylactic group was given cows' milk formula in the nursery by mistake and 10 mothers found the diet too restrictive and gave up within the first 4 weeks (in most within the first few days). These infants were not followed up. In the control group, 3 mothers did not attend the follow-up clinic and 2 left the area.

In the prophylactic group, lactating mothers followed a strict dietary regimen that excluded dairy products, egg, fish, and nuts. Up to 9 months breastfeeds were supplemented, if necessary, with a soya-based protein hydrolysate (Aptamil HA, Milupa, UK). Formula-fed infants received Aptamil HA from birth. The infants' diet was free of dairy products, egg, wheat, soya (unhydrolysed), orange, fish, and nuts. Cows' milk and soya were introduced at 9 months, wheat at 10 months, and egg at 11 months. After 12 months there was no restriction on the infants' diet. A dietitian explained the dietary restrictions in detail to all mothers when their infants were born. Written instructions were also provided with a list of foods to take and to avoid at various stages for both mother and infant. All lactating mothers were provided with calcium (1000 mg/day) and vitamin supplements.

The prophylactic group also avoided housedust-mite antigen. All infants used polyvinyl-covered mattresses with vented head area. The infants' homes were visited during the first week of life. In each home, nurses collected dust samples, by means of a hand-held mains-operated (500 W) vacuum cleaner (Hoover, UK) with dust filters (ALK, Denmark), from the infants' bedroom carpet, the living-room carpet, and upholstered furniture. No significant amounts of dust were obtained from covered mattresses. Antidust-mite treatment with Acarosan (Crawford Chemicals, UK) foam and powder was applied to the infant's bedroom carpet, living-room carpet, and upholstered furniture. This procedure was repeated every 3 months to 9 months. Dust samples were analysed by a sandwich-type enzyme-linked immunosorbent assay with monoclonal-antibody-labelled discs (ALK, Denmark) for the main antigen of *Dermatophagoides pteronyssinus* (*Der p* I).

Mothers and infants in the control group followed a normal diet advised by their health-visitors. The homes of control-group infants were visited soon after delivery and at 9 months of age for collection of dust samples for *Der p* I measurement.

All infants and mothers attended hospital clinics at 3 and 6 months. Any symptoms and signs related to allergic disorder were recorded and appropriate advice was given. Further visits were arranged if necessary for assessment of any allergy-related disorders. A dietitian assessed the nutritional adequacy of the diet for infants and mothers in the prophylactic group. Compliance with the prophylactic regimen was checked by questioning of the mother, regular home visits by research nurses, and analysis of breastmilk samples for cows' milk protein (bovine casein and lactoglobulin). Between 4 and 12 weeks, 8 mothers gave up the diet. 3 infants were introduced to cows' milk and wheat between 24 and 32 weeks. These infants were included in the final analysis.

At 10–12 months, a paediatric allergy specialist unaware of group allocation examined all children for allergic disorders. Asthma was defined as three or more separate episodes of cough and wheezing and eczema as chronic or chronically relapsing dermatitis (lasting more than 6 weeks) with characteristic morphology (areas of scaly, erythematous, pruritic lesions) and distribution (face, postauricular area, scalp, extensor surface of arms and legs, and flexural creases). Food intolerance was defined as a history of vomiting, diarrhoea, colic, or rash within 4 h of ingestion of a recognised food allergen. The food was excluded from the diet for 4 weeks and a diagnosis of food intolerance was accepted if symptoms recurred on open challenge. All skinprick tests were done by one research nurse with allergen extracts (Soluprick ALK, Denmark) against housedust mite, grass pollen, cat dander, cows' milk, egg, and any other allergen implicated in a particular case. A mean wheal diameter (half the sum of largest diameter and its perpendicular) of more than 2 mm but at least half the size of the wheal produced with histamine was regarded as positive.

Information on the presence of pets and parental smoking habits was obtained at the prenatal visit and updated at each visit. Parents were regarded as smokers if they regularly smoked one or more

TABLE I—CHARACTERISTICS OF STUDY GROUPS

—	Prophylactic (n = 58)	Control (n = 62)
No included with		
Dual heredity	51	42
Single heredity plus high IgE	7	20
No with allergy in		
Mother	42	41
Father	31	34
Sibling	36	31
Mean cord-blood IgE (kU/l)		
25th percentile	0·34	0·49
50th percentile	0·65	0·66
75th percentile	0·85	0·81
90th percentile	0·95	0·93
Male/female	28/30	34/28
No with smoking by		
Mother	8	16
Father	21	22
Either	21	27
No in socioeconomic group		
High (A, B, C)	30	33
Low (D, E)	28	29
No sharing bedroom	26	25
No with pets in household	36	38

TABLE II—INFANT FEEDING PRACTICES

—	% of group	
	Prophylactic	Control
Breastfeeding		
From birth	71	77
At 3 mo	43	48
At 6 mo	28	31
At 9 mo	17	15
*Formula feeding**		
1 mo	50	44
3 mo	78	71
6 mo	88	84
Solid foods		
3 mo	40	48
6 mo	97	97

*Aptamil HA in prophylactic group and cows' milk formula in controls.

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cigarettes a day. Birthweight was recorded and infants were weighed at each visit. Information was also obtained on social class (classified by father's occupation except when the mother was single or the father unemployed and the mother employed) and whether the infant shared a bedroom with parents or other children. The social classes were defined according to the Registrar-General's classification. Analysis was done with classes 1, 2, and 3 grouped together as the higher socioeconomic group and classes 4 and 5 as the lower socioeconomic group.

We sought a 50% reduction in allergic disorder in the prophylactic group. This large reduction combined with the likely high incidence of allergy in this population meant that at least 60 infants were required in each group to give 80% power of detecting a difference at 5% significance. For *Der p* I, comparison of group means was done by the unpaired *t* test and means within groups were compared by the paired *t* test. Logistic regression analysis was used to assess the independent contribution of factors to the risk of allergic disorders. The presence of any allergic disorder at 3, 6, and 12 months' follow-up and individual allergic disorders at 12 months was used as the dependent variable. All risk factors of interest were included in the model and significance was tested for each one, with control for all other factors, by means of the Wald statistics. Adjusted odds ratios with 95% confidence intervals (CI) were calculated. Statistical analysis was done with SPSS/PC+ V4 (SPSS, Chicago, Illinois, USA).

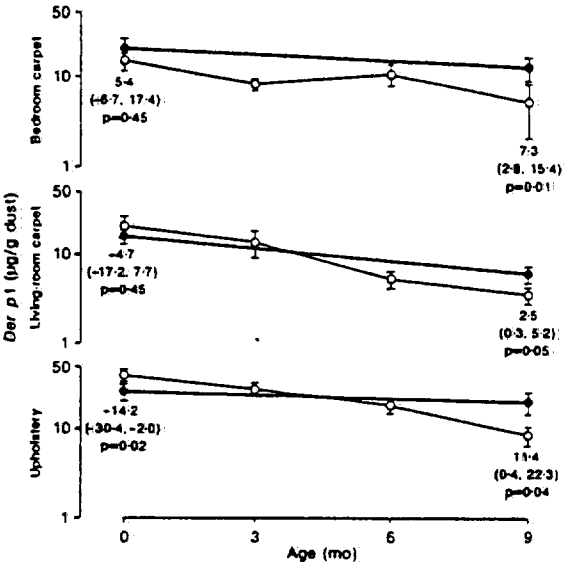
Results

The two groups had similar heredity characteristics, cord-blood IgE distribution, and home environments (table I). Rates of breastfeeding, formula feeding, and introduction of solid foods were similar in the two groups (table II). All infants gained weight satisfactorily; for example, at 3 months the mean (SD) weight was 5·62 (0·84) kg in the prophylactic group compared with 5·73 (0·84) kg in the control group, and at 12 months the groups' respective mean weights were 9·18 (1·15) kg and 9·56 (1·34) kg. The growth pattern of infants fed Aptamil HA from birth was similar to that of the rest of the group (data not shown).

The measures to reduce concentrations of *Der p* I in the homes of the prophylactic group were successful in that the concentrations were significantly lower than those of the control group at 9 months (see figure). In the prophylactic group, the mean *Der p* I concentration for upholstery and living-room and bedroom carpets was 25·9 µg/g dust at birth and 6·0 µg/g dust at 9 months.

By the age of 12 months one or more allergic disorders had developed in 25 (40%) control children and 8 (14%) prophylactic-group children. Although the doctor who made follow-up assessments at 3 and 6 months was aware of group allocation, the pattern was similar (3 months control 18% *vs* prophylactic 5%; 6 months 32% *vs* 12%). Signs of asthma were present at 12 months in 12 (19%) infants in the control group and 4 (7%) of the prophylactic group. The corresponding numbers for eczema were also 12 (19%) and 4 (7%). 7 (11%) control-group infants were classified as having food intolerance, in most to cows' milk or egg, at 12 months. Only 2 (3%) infants in the prophylactic group had food intolerance: in 1 a rash developed when egg was introduced at the age of 7 months; and the other infant had asthma and wheezed after drinking cows' milk when Aptamil HA was stopped at 9 months. 6 (10%) infants in the control group had positive skinprick tests to a range of allergens including housedust mite, cows' milk, egg, wheat, cat, and grass pollen. 2 (3%) infants in the prophylactic group showed positive skinprick tests—1 to egg and 1 to cat dander.

To control for possible effects, despite randomisation, of genetic and environmental factors and to assess the influence



Mean (SEM) *Der p* I concentrations in prophylactic (○) and control (●) groups.

Boxes show mean and (95% CI) difference between groups.

of other risk factors on the development of allergic disorders, we carried out multivariate logistic regression analysis to obtain the adjusted odds ratios for each factor. Logistic regression was done with the presence of any allergic disorder at 3, 6, or 12 months as the dependent variable and all risk factors of interest as independent variables (table III). The process was repeated with individual allergic disorders (at 12 months) as the dependent variables (table IV). After adjustment for other confounding variables, the control group was at significantly greater risk than the prophylactic group for all allergy at each follow-up examination and for asthma and eczema at 12 months. Parental smoking was the other important risk factor irrespective of whether only one or both parents smoked in the house. Maternal smoking was not used as a separate variable, since only 5 mothers smoked and had partners who did not. As expected, maternal allergy, sibling allergy, and male sex were other significant risk factors for total allergy. The prevalence of all allergy at

TABLE III—EFFECT OF RISK FACTORS ON PREVALENCE OF TOTAL ALLERGY

Risk factor	Reference group	Odds ratio (95% CI) 3 mo	6 mo	12 mo
Control group	Prophylactic group	5·64 (1·3–24·2)*	3·98 (1·4–11·5)†	6·34 (2·0–20·1)‡
Parental smoking				
Either	Neither	1·25 (0·2–6·4)	3·36 (1·1–10·7)*	3·97 (1·2–13·6)*
Both	Neither	5·12 (1·2–22·5)*	1·81 (0·5–6·9)	4·72 (1·2–18·2)*
Allergy in				
Mother	No such allergy	2·38 (0·5–11·8)	3·16 (0·9–11·9)	5·92 (1·5–23·0)†
Sibling	No such allergy	1·69 (0·4–6·9)	1·36 (0·5–4·0)	4·59 (1·3–15·8)*
Male	Female	4·17 (1·0–18·3)*	1·93 (0·7–5·5)	1·44 (0·5–4·2)
Low socio-economic group	High socio-economic group	1·43 (0·4–5·4)	1·41 (0·5–4·0)	3·30 (1·1–10·2)*

*p < 0·05, †p < 0·01, ‡p < 0·005, for comparison with reference group.

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TABLE IV—EFFECT OF RISK FACTORS ON PREVALENCE OF CERTAIN ALLERGIC DISORDERS AT 12 MO

Risk factor	Reference group	Odds ratio (95% CI)		
		Asthma	Eczema	Food intolerance
Control group	Prophylactic group	4·13 (1·1–15·5)*	3·59 (1·0–12·5)*	3·29 (0·6–17·3)
Parental smoking				
Either	Neither	3·33 (0·8–14·6)	2·35 (0·7–7·9)	1·46 (0·2–9·7)
Both	Neither	11·07 (2·5–48·2)†	0·88 (0·2–5·6)	5·72 (1·1–29·5)*
Sibling allergy	No such allergy	5·71 (1·3–24·5)*	1·39 (0·4–4·5)	0·74 (0·2–3·7)

*$p < 0.05$, †$p < 0.005$.

12 months was higher in infants from the lower than the higher socioeconomic group. Factors tested but found not to be significant, or to change odds ratios for other variables were paternal allergy and the presence of pets (for total allergy), and male sex, maternal or paternal allergy, socioeconomic group, and presence of pets for individual allergic disorders.

Discussion

Since seasonal factors can affect the development of allergic disorders[4,5] we received mothers and their infants for a whole year. A study of the effect of treatment should ideally be double blind, but the nature of the intervention in our study made this ideal impossible. The final assessment by the paediatric allergy specialist was done "blind"; all mothers were briefed before they entered the consulting room not to disclose their group allocation.

At present, allergen avoidance is recommended for treatment but not for prophylaxis of allergic disorders. Because prophylactic measures take much time and effort, only infants at high risk of atopy are suitable for this kind of intervention. Exposure to highly allergenic food and inhalant antigenic protein could prime the immune systems of genetically predisposed infants. Transplacental sensitisation is rare; specific IgE is rarely found in cord blood.[18,19] Two studies[15,20] showed no benefit from food avoidance during the third trimester of pregnancy. Moreover, such avoidance adversely affected weight gain during third trimester and resulted in a slightly lower than expected birthweight for the term infants.

Previous studies[15,17] have shown lower rates of eczema and food reactions when mothers of at-risk infants restrict their diets during lactation. In our study, exposure to allergenic foods, either directly or through mothers' milk, was avoided up to 12 months of age. It is possible that a shorter duration of exclusion is sufficient. Exclusion of the 11 infants whose diets were violated from the analysis did not affect the outcome. In the nursery, cows' milk formula was given inadvertently to a few infants in the prophylactic group. Mistakes were generally avoided by close cooperation with midwives, warning stickers on infants' cots and mothers' beds, and education of mothers to be very vigilant. During the study 16 mothers reported occasional mistakes, such as drinking a cup of tea with milk or giving the infant a manufactured food containing soya or casein. Overall, compliance was very good for such a difficult diet. For mothers who did not wish to breastfeed or who wanted to supplement breastmilk, Aptamil HA was a useful alternative. It is made from soya and collagen and is extensively hydrolysed. The molecular weight of 99% of the molecules is less than 10^4 Da. Similar hydrolysed milk is used for the treatment of cows' milk allergy and can reduce the incidence of eczema and food reactions.[15,17]

Previous studies[15-17] have concentrated on food-allergen avoidance and have reported reductions in eczema and food reactions but not in respiratory symptoms. Inhalant allergens and adjuvants are equally important,[2-9] although more difficult to control. In the UK, housedust mite is the most common allergen in patients with extrinsic asthma and atopic eczema. Chemicals are now available that not only kill the mites but also help to reduce the level of antigen already present in the carpet.[21] Repeated use of one such acaricide in this study gradually reduced antigen concentrations. For prophylaxis, acaricide applications should perhaps be started a few months before the infant is born. The design of our study means that the effect of food and housedust-mite avoidance cannot be separated. Ideally, we should have asked parents in the prophylactic group to give up smoking and to remove furry pets from the house. We did not attempt these interventions for fear of non-compliance, and no advice was offered to either group on pets and smoking in the house.

In infancy, bronchial hyperreactivity manifests as recurrent cough and wheeze, usually after viral respiratory-tract infections. It has been termed recurrent wheezing, wheezy bronchitis, infantile wheezing, and asthma. We prefer to use the term asthma, since many affected infants are later found to be atopic/asthmatic,[22] especially those with genetic predisposition;[23] others, however, disagree with this classification.[24] Sporik and colleagues[6] found that onset of wheezing was earlier in atopic children exposed to high levels of dust-mite antigen in infancy than in those not so exposed. Perhaps in genetically predisposed infants with high allergen exposure, viral respiratory infections and smoking act as adjuvants and lead to persistent bronchial hyperreactivity and asthma.

For practical reasons, open challenge was used for the diagnosis of food intolerance. A double-blind challenge would have been more reliable but management of any adverse food reactions reported by the mother was the same in both groups and blind assessment should have reduced any possible bias. We avoided the term food allergy, since evidence for IgE-mediated food allergy (positive skinprick test to the relevant food antigen) was available in only 30% of cases. A positive skinprick test without signs of allergy (in 1 infant in the prophylactic group, to egg) was not regarded as an allergic manifestation. Chronic "cold" and runny nose were reported in 17 infants (7 prophylactic, 10 control) at 12 months' follow-up. We did not include these signs in the analysis since their aetiology and clinical significance are difficult to establish. No infant with these signs had a positive skinprick test to inhalant allergens.

Individual disorders were two to three times more common in the control than in the prophylactic group and the prevalences of asthma and eczema were higher at 12 months. Parental smoking had a profound effect on the prevalence of asthma and total allergy. In some of the infants asthma may represent transient bronchial hyperreactivity, but we cannot exclude the possibility of continued wheezing in a substantial proportion of these genetically predisposed infants. Advice on parental smoking should be included in any prophylactic regimen against allergic disorders.

We conclude that reduction in exposure of high-risk infants to food and housedust-mite allergens substantially lowers the frequency of allergic manifestations in infancy. Parental smoking contributes greatly to the development of

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allergic disorders during infancy and should be avoided, especially in genetically predisposed families. It is possible that allergen avoidance merely delays rather than prevents the development of allergic disorders.[25] In our study foods were introduced at age 9–12 months in the prophylactic group and only 1 infant reacted to cows' milk. Longer follow-up is required, at least into later childhood, to find out whether the reduction in allergic manifestations will be maintained. Because of their high prevalence, allergic disorders are a huge burden to personal and family life and a substantial health-care cost. If the benefit shown in this study is maintained, it is likely to outweigh the costs of dietary supervision, hypoallergenic formulae, and antidust-mite measures.

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Effects of topical nasal anaesthesia on shift of breathing route in adults

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The position of the soft palate is known to determine the breathing route, but the physiological mechanisms that bring about a shift from nasal to oral breathing are unclear. To test the hypothesis that activation of receptors in the nasal passage may be involved in reflex initiation of oral breathing after nasal obstruction, we investigated respiratory responses to nasal occlusion before and after topical lignocaine anaesthesia of the nasal passages.

Eleven volunteers were fitted with custom-made partitioned face masks, which separated nasal and oral passages. Air flow through each passage was detected by changes in airway pressure and carbon dioxide concentration. Nine subjects were habitual nasal breathers both before and after topical anaesthesia with 4% lignocaine. Among these subjects, the time to initiate oral breathing in response to nasal occlusion was significantly shorter before anaesthesia than afterwards (mean 4·4 [SD 2·5] *vs* 10·8 [7·4] s, $p<0·01$). Similarly, the time to resume nasal breathing after release of nasal occlusion was significantly shorter before topical anaesthesia than afterwards (6·9 [4·9] *vs* 12·1 [7·8] s, $p<0·01$). Topical anaesthesia did not affect respiration rate, end-tidal carbon dioxide concentration, or arterial oxygen saturation.

These findings suggest that in human beings sensory information from receptors in the nasal passage has an important role in controlling the shift of breathing route.

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